REMARKS/ARGUMENTS

I. Status of the claims

Claims 25-41 are currently pending. Claims 34-41 have been withdrawn by the Examiner. Claims 25-33 are being examined.

II. Information Disclosure Statement

The Examiner states that the information disclosure statement filed 8/16/2004 fails to comply with 37 CFR 1.98(a)(2), and that the copies of cited foreign patent documents and the non-patent literature publications are not found in the parent case 10/133,128.

On April 6, 2007, Applicants filed, in the present application, a Supplemental Information Disclosure Statement, Form PTO/SB/08 and copies of cited foreign patent documents and non-patent literature publications that were listed on the information disclosure statement filed 8/16/2004.

Enclosed herewith is another Supplemental Information Disclosure Statement, Form PTO/SB/08 and copy of a cited non-patent literature publication.

Applicants respectfully request that each document listed on the Form PTO/SB/08 filed on April 6, 2007, as well as the document listed on the Form PTO/SB/08 filed concurrently herewith, be considered by the Examiner and be made of record in the present application, and that an initialed copy of these Forms be returned in accordance with MPEP §609.

III. Oath/Declaration

The Examiner asserts that the oath or declaration is defective because it does not identify the mailing address, city and either state or foreign country of residence of inventor Per-Ola Fresgard, and indicated that the missing information may be provided on either an application data sheet or supplemental oath or declaration.

Attached hereto is an application data sheet which includes the information requested by the Examiner.

IV. Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 25-33 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description and enablement requirements.

A. The Claimed Invention

Claim 25 is the only independent claim currently under examination by the Examiner. All other claims under examination are dependent either on claim 25 or another dependent claim. Accordingly, the discussion below focuses on claim 25.

25. A method for identifying a multimer that binds to a target molecule, the method comprising,

providing a library of polypeptides, the polypeptides comprising different monomer domains, wherein the monomer domains have 30-100 amino acids;

screening the library of polypeptides for affinity to a target molecule;

identifying at least a first polypeptide comprising a first monomer domain that specifically binds to a target molecule;

linking the first monomer domain to a plurality of different monomer domains to form a library of different multimers, the multimers comprising the first monomer domain and one of the plurality of different monomer domains;

screening the library of multimers for the ability to bind to the target molecule; and

identifying a multimer that specifically binds to the target molecule, wherein the multimer comprises the first monomer domain and a second monomer domain.

B. Analysis – Written Description

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., Moba, B.V. v. Diamond Automation, Inc., 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003); Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563, 19 USPQ2d at 1116. Possession may be shown in a variety of ways including description of an actual reduction to practice. See, e.g., Pfaff v. Wells Elecs., Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998).

In the present case, the Applicants have shown actual reduction to practice of the claimed invention. Claim 25 encompasses a method referred to as to as "walking", described, *e.g.*, at paragraph 230 on page 65 of the specification:

> [230] When multimers capable of binding relatively large targets are desired, they can be generated by a "walking" selection method. This method is carried out by providing a library of monomer domains and screening the library of monomer domains for affinity to a first target molecule. Once at least one monomer that binds to the target is identified, that monomer is covalently linked to a new library or each remaining member of the original library of monomer domains. This new library of multimers (dimers) is then screened for multimers that bind to the target with an increased affinity, and a multimer that binds to the target with an increased affinity can be identified. The "walking" monomer selection method provides a way to assemble a multimer that is composed of monomers that can act additively or even synergistically with each other given the restraints of linker length. This walking technique is very useful when selecting for and assembling multimers that are able to bind large target proteins with high affinity. The walking method can be repeated to add more monomers thereby resulting in a multimer comprising 2, 3, 4, 5, 6, 7, 8 or more monomers linked together.

Applicants have actually reduced the claimed method to practice. For instance, Example 11 (pages 107 to 111 of the specification) describes the development of CD28-specific LDL receptor-based A domains and dimers by "walking." The steps followed in this Example follow the steps of the method claimed in the present invention. The applicants provided a library of DNA sequences encoding monomeric A domains. The applicants screened the library of polypeptides for affinity to a target molecule by coating individual wells of a 96-well microtiter plate with target protein (e.g., CD28) and after blocking, adding purified phage and incubating followed by washing. Bound phages were eluted and the phage eluate was amplified to identify at least a first polypeptide comprising a first monomer domain that specifically binds to a target molecule. The monomer fragments were then 'walked' to dimers by attaching a library of naive A domain fragments using DNA ligation, thereby forming a library of different multimers, the multimers comprising the first monomer domain and one of the plurality of different monomer domains. The multimer library was then screened as described above, and

binding of the individual phage clones to their target proteins was analyzed by ELISA. Multimers were thus identified which specifically bound to the target molecule, where the multimer comprises the first monomer domain and a second monomer domain. As further described in Example 11; a subset of these clones was then used in efficacy assays using human and monkey PBMC, and demonstrated inhibition activity in those assays.

The Examiner asserts that the instant claims are drawn to a genus of polypeptides comprising a genus of monomers (or monomer domains), as well as to a genus of multimers that are comprised of the monomers. Contrary to what is implied by the Examiner, the present claims are drawn *not* to polypeptides or library compositions, but rather, to *methods* for identifying a multimer that binds to a target molecule. This is an important distinction – the Applicants are not attempting to claim, in this application, the libraries, monomers, multimers, or any other compositions that may be used in connection with the claimed method. Rather, the claims are directed to *methods*, and are applicable for use in connection not only with monomer libraries that one of skill in the art may generate based on the present specification, but also pre-existing libraries which may be modified following the guidance in the specification (e.g., "walked" from a monomer library to a dimer library) or libraries that may be made in the future and then used in accordance with the methods of the present invention.

In view of the foregoing, the Applicants maintain that the pending claims comply with the written description requirement, and respectfully request withdrawal of the rejections under 35 U.S.C. §112, first paragraph

C. *Analysis – Enablement*

To satisfy the enablement requirement, the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'. In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted. In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). All that is necessary is that one skilled in the art be able to practice the claimed invention, given the

level of knowledge and skill in the art.

In the present case, the invention is based on a particularly advantageous method of developing libraries of multimers having an enhanced representation of desired molecular entities. As described in the specification, this method is carried out by providing a library of monomer domains and screening the library of monomer domains for affinity to a first target molecule. Once at least one monomer that binds to the target is identified, that monomer is covalently linked to a set of different monomer domains. The resulting new library of multimers (e.g., dimers) is then screened for multimers that bind to the target with an increased affinity, and a multimer that binds to the target with an increased affinity (relative to the affinity of the initial monomer) can be identified.

The Applicants do not claim to have discovered the generic notion of combinatorial libraries or the screening thereof. Indeed, the art of combinatorial libraries is well-known and established in basic research as well as industry. For example, as stated in the abstract and opening paragraph of Liu, *et al.*, "Combinatorial peptide library methods for immunobiology research", *Experimental Hematology* **31**:11-30 (2003):

> The field of combinatorial peptide chemistry has emerged as a *powerful tool in the study of many biological systems*.... These peptide libraries have successfully been employed to study a vast array of cell surface receptors, as well as have been useful in identifying protein kinase substrates and inhibitors. In recent immunobiological applications, peptide libraries have proven monumental in the definition of MHC anchor residues, in lymphocyte epitope mapping, and in the development of peptide vaccines. .... *Combinatorial peptide libraries offer a high-throughput approach to study limitless biological targets*. Peptides discovered from such studies may be therapeutically and diagnostically useful agents.. Abstract; Emphasis added.

> Nowadays, virtually every major pharmaceutical company has an in-house combinatorial chemistry program. In addition to being an *indispensable tool for drug discovery*, combinatorial chemistry is a great tool for basic research. Ligands or inhibitors for a variety of target proteins can be discovered.. Opening paragraph; Emphasis added.

One of skill in the art will appreciate that the claimed method is applicable in situations where one has or can obtain or create a library of monomer domains. Such libraries, and generic methods for screening them, are well-known in the art (see above). Given this base

of knowledge available to one of skill in the art for libraries in general, the applicants have described, enabled and claimed a novel method for screening such libraries using the claimed walking approach as summarized above. This novel method may, as mentioned previously, be applied to any of a number of libraries known to one of skill in the art.

The examiner states that the while the specification is enabling for generating libraries of monomers and/or multimers based on LDL receptor A domains and C2 domains, it does not reasonably provide enablement for generating other proteins that comprise any other monomers or multimers. The examiner cites a reference (Roodveldt, et al.) as allegedly teaching that "the stability of proteins, especially heterologous proteins, is highly unpredictable and that [such proteins] may not be expressed or made properly"... "Thus, the stabilities of proteins with various amino acid sequences are highly unpredictable, and hence the success of generating such proteins is also unpredictable" (Office action mailed 11/13/2006, page 13, lines 1-2; 8-9). The Applicants respectfully submit that the relevant analysis concerns libraries, and not the stability of proteins in general. For example, if a particular molecule in a library of many such molecules is not expressed or is unstable, it may not be present or functional in the library. This does not mean, however, that the library itself is unpredictable or unstable. Indeed, the widespread use and adoption of libraries, both in research hand industry, would seem to contradict the Examiner's conclusion (the success of generating such proteins [with various amino acid sequences] is unpredictable") and suggests the ability to generate functional libraries is to a large extent predictable and well within the knowledge of one of skill in the art. This knowledge in the art and predictability of libraries in general, combined with the guidance provided by the Applicants in the specification in connection with the claimed "walking" method, thus serve to provide a fully-enabling disclosure for the claimed invention.

In view of the foregoing, the Applicants respectfully submit that the pending claims under examination comply with both the written description and enablement requirements, and respectfully request withdrawal of the rejections under 35 U.S.C. §112, first paragraph.

V. Rejections under 35 U.S.C. § 102

The Examiner rejected claims 25, 27, 28, 30, 31, and 33 under 35 U.S.C. §102(b) as anticipated by Barbas, *et al.* (US 6,140,466; 10/31/2000). The Examiner further rejected claims 25-30, 32, and 33 under 35 U.S.C. §102(b) as anticipated by Esser, *et al.* (Journal of Biological Chemistry. Vol. 263: 13282-13290; 1988). The Examiner further rejected claims 25-33 under 35 U.S.C. §102(b) as anticipated by Bajari, *et al.* (Biological Chemistry. Vol. 379: 10153-10162; 1998). The Examiner further rejected claims 25-31 and 33 under 35 U.S.C. §102(e) as anticipated by Etzerodt, *et al.* (US 2004/0132094 A1; 7/8/2004; alleged priority date: 2/28/2001).

A. The Present Invention

See "*The Claimed Invention*" under Section IV(A), above.

B. Barbas, *et al.*

Barbas, *et al.*, teach a polypeptide linker that fuses two three-finger Zinc finger proteins -- two six-fingered proteins were created and demonstrated to bind 18 contiguous bp of DNA in a sequence specific fashion. Barbas, *et al.*, further teach that expression of these proteins as fusions to activation or repression domains allows transcription to be specifically up or down modulated within cells, and that polydactyl zinc finger proteins are broadly applicable as genome-specific transcriptional switches in gene therapy strategies and the development of novel transgenic plants and animals. Barbas, *et al.*, additionally disclose that such proteins are useful for inhibiting, activating or enhancing gene expression from a zinc finger-nucleotide binding motif containing promoter or other transcriptional control element, as well as a structural gene or RNA sequence. Barbas, et al., also teach a method for obtaining an isolated zinc finger-nucleotide binding polypeptide variant which binds to a cellular nucleotide sequence, comprising identifying the amino acids in a zinc finger-nucleotide binding polypeptide that bind to a first cellular nucleotide sequence and modulate the function of the nucleotide sequence; creating an expression library encoding the polypeptide variant containing randomized substitution of the amino acids identified; expressing the library in a suitable host cell; and isolating a clone that

produces a polypeptide variant that binds to a second cellular nucleotide sequence and modulates the function of the second nucleotide sequence.

Barbas, et al., do not teach screening the library of polypeptides for affinity to a target molecule, identifying at least a first polypeptide comprising a first monomer domain that specifically binds to a target molecule, linking the first monomer domain to a plurality of different monomer domains to form a library of different multimers, the multimers comprising the first monomer domain and one of the plurality of different monomer domains, and screening the library of multimers for the ability to bind to the target molecule.

C. Esser, *et al.*

Esser, *et al.*, teach a mutational analysis of the ligand binding domain of the low density lipoprotein (LDL) receptor. According to Esser, *et al.*, the ligand binding domain of the LDL receptor contains seven imperfect repeats of a 40-amino acid cysteine-rich sequence (referred to by Esser, *et al.*, as Repeats 1-7). To dissect the contribution of these different cysteine-rich repeats to ligand binding, Esser, *et al.*, used oligonucleotide-directed mutagenesis to generate nine substitution mutations (each as a separate construct) in the ligand binding domain.

Esser, et al., do not teach screening the library of polypeptides for affinity to a target molecule, identifying at least a first polypeptide comprising a first monomer domain that specifically binds to a target molecule, linking the first monomer domain to a plurality of different monomer domains to form a library of different multimers, the multimers comprising the first monomer domain and one of the plurality of different monomer domains, and screening the library of multimers for the ability to bind to the target molecule.

D. *Bajari, et al.*

Bajari, *et al.*, define the minimal binding domain of the multifunctional chicken oocyte receptor for yolk deposition (termed LR8), a relative of the low density lipoprotein receptor (LDLR). Bajari, *et al.*, used phage display of fragments derived from the entire LR8 receptor molecule and panning on the ligand -- receptor associated protein (RAP) -- to define an

80 residue stretch LR8 minireceptor. The 80 residue stretch contains 12 cysteines, and represents parts of the second, the entire third, and parts of the fourth, of the eight clustered 'ligand binding repeats' in LR8. Bajari, *et al.*, state that in addition to its use in defining minimal binding domains, the phage display approach provides powerful tools for dissection, and consequently, manipulation, of the function of receptors so as to direct their binding activity toward ligands of diagnostic and/or therapeutic interest. The reference also teaches that the phage display method is adaptable to rapid analysis of in vitro mutagenized receptor fragments in order to obtain soluble minireceptors that may interact with a defined subset of ligands, and states that LR8 is an ideal substrate to perform such studies due to its being the smallest known member of the LDLR family that can bind all of the ligands of the family identified so far.

Bajari, *et al.*, do not teach screening the library of polypeptides for affinity to a target molecule, identifying at least a first polypeptide comprising a first monomer domain that specifically binds to a target molecule, linking the first monomer domain to a plurality of different monomer domains to form a library of different multimers, the multimers comprising the first monomer domain and one of the plurality of different monomer domains, and screening the library of multimers for the ability to bind to the target molecule.

E. *Etzerodt, et al.*

Etzerodt, *et al.,* teach a family of protein libraries comprising CTLDs (C-type Lectin-Like Domains), e.g., Tetranectin CTLDs, in which internal polypeptide loop-regions lining the ligand binding sites in CTLDs have been replaced with ensembles of completely or partially randomized polypeptide segments. Etzerodt, *et al,*. further teach the generation and manipulation of human and murine tetranectin CTLD libraries, as well as phagemid vectors useful in the generation and manipulation of human and murine tetranectin CTLD libraries. The reference also teaches that CTLD derivatives with affinity for new ligands may readily be isolated from libraries of vectors displaying CTLDs, in which loop-regions have been randomized, using one or more rounds of enrichment by screening or selection followed by amplification of the enriched subpopulation in each round.

Etzerodt, *et al.*, do not teach screening the library of polypeptides for affinity to a target molecule, identifying at least a first polypeptide comprising a first monomer domain that specifically binds to a target molecule, linking the first monomer domain to a plurality of different monomer domains to form a library of different multimers, the multimers comprising the first monomer domain and one of the plurality of different monomer domains, and screening the library of multimers for the ability to bind to the target molecule.

F. *Analysis*

For anticipation under 35 U.S.C. §102, a single reference must teach every aspect of the claimed invention. The methods encompassed by the claimed invention are directed to the making and screening of a "walked" multimer library, where the multimer library was generated using monomer domain(s) that bound to a first target molecule and linking such a first monomer domain to a plurality of different monomer domains to form a library of different multimers. None of Barbas, *et al.*, Esser, *et al.*, Bajari, *et al.*, or Etzerodt, *et al.*, teach such "walked" libraries or methods of using them to identify a multimer (or any molecule) that binds to a target molecule. Since none of these references teach these elements of the claimed methods, the Applicants respectfully submit that none of Barbas, *et al.*, Esser, *et al.*, Bajari, *et al.*, or Etzerodt, *et al.*, anticipate the pending claims. In view of the foregoing, the Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §102.

VI. Rejections under 35 U.S.C. § 103

The Examiner rejected claims 25-33 under 35 U.S.C. §103(a) as unpatentable over Esser, *et al.* (Journal of Biological Chemistry. Vol. 263: 13282-13290; 1988), in view of Bajari, *et al.*, (Biological Chemistry. Vol. 379: 10153-10162; 1998).

A. *The Present Invention*

See above.

B. *Esser, et al.*

See above.

C. *Bajari, et al.*

See above.

D. *Analysis*

As noted above, the primary reference of Esser, *et al.*, does not teach any "walked" libraries or any methods of using such walked libraries. This failing is not remedied by the secondary references of Bajari, et al. The references cited by the Examiner provide neither the elements of nor any motivation or suggestion to arrive at the methods of the present invention.

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so. *In re Kahn*, 441 F.3d 977, 986 (Fed. Cir. 2006). Rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. *Id.* at 988. In the present case, the Examiner has failed to provide references teaching the elements of the invention and has not articulated any reasoning or rationale to arrive at the claimed invention or to support the Examiner's conclusion of obviousness.

In view of the foregoing, the Applicants respectfully request withdrawal of the rejection(s) under 35 U.S.C. §103.

VII. Double Patenting

The Examiner provisionally rejected claim 25-33 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11, 15-17, and 20-26 of copending Application No. 11/281,256 (200602342 99; filed 11/16/05).

The Examiner provisionally rejected claim 25-33 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-28 of copending Application No. 11/281,245 (20060223114; filed 11/06/05).

The Examiner provisionally rejected claim 25 and 33 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 207-214 of copending Application No. 10/966,064 (20050221384; filed 10/15/04).

The Examiner provisionally rejected claim 25-33 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 21-32 of copending Application No. 10/971,679 (20050164301; filed 10/22/04).

The Examiner provisionally rejected claim 25-33 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 5-11, 21, 29, 33, 36, 78, and 98 of copending Application No. 10/871,602 (20050089932; filed 6/17/04).

The Examiner provisionally rejected claim 25-33 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 5-11, 13, 16, 23, 29, 33, 36, 78, and 98 of copending Application No. 10/840,723 (20050053973; filed 5/5/2004).

The Examiner provisionally rejected claim 25, 26, and 28-33 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 18, 21-24, 29-31 and 34-36 of copending Application No. 10/957,351 (20060008844; filed 1/12/2006).

The Examiner provisionally rejected claim 25-33 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 15, 18-21, and 24-27 of copending Application No. 11/155,989 (20060177831; filed 6/17/05).

The present application was filed on 10/24/2003. Where a provisional nonstatutory obviousness-type double patenting rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application may be rejectable on other grounds, the MPEP (§804) instructs the Examiner to withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer. Accordingly, the Applicants respectfully request the Examiner to withdraw this provisional nonstatutory obviousness-type double patenting rejection and allow this application to issue.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 650-244-3147.

The Commissioner is hereby authorized to charge any additional fees which may be required or credit any overpayment to Deposit Account No. 01-0519 in the name of Amgen Inc.

Respectfully submitted,

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